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Endoplasmic Reticulum Stress in Rheumatoid Arthritis: Mechanisms, Pathogenic Roles, and Therapeutic Opportunities

Anastasia V. Poznyak [1]*, Nikolay Konstantinovich Shakhpazyan[2], Olga Nikolaevna Maltseva[3], Elizaveta Romanovna Korchagina[1], Alexander N. Orekhov [1]

[1] Institute for Atherosclerosis Research, Osennyaya 4-1-207, 121609 Moscow, Russia

[2]Avtsyn Research Institute of Human Morphology, Petrovsky National Research Centre of Surgery, 3 Tsyurupa Street, 117418 Moscow, Russia

[3]Institute of Experimental Medicine, 12, Academician Pavlov Street Street, 197022, Saint Petersburg, Russia

[4]Department of Commodity Expertise and Customs Business, Plekhanov Russian University of Economics, 36, Stremyanny Lane, 115054 Moscow, Russia

***Corresponding authore**

Email ID : tehhy_85@mail.ru (AVP)

ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent inflammation, synovial hyperplasia, and joint destruction. Accumulating evidence implicates endoplasmic reticulum stress (ERS) and the unfolded protein response (UPR) as key contributors to RA pathogenesis. This review consolidates recent findings on how ERS-related pathways—including PERK-eIF2α-ATF4, IRE1-XBP1, and ATF6—interact with immune, inflammatory, and apoptotic mechanisms in RA. It also examines the molecular connections between HLA-linked susceptibility, protein citrullination, and synovial cell dysfunction. Persistent ERS promotes synoviocyte proliferation, cytokine production, and angiogenesis, sustaining chronic inflammation and tissue damage. Targeting UPR mediators such as GRP78, PERK, and IRE1 shows promise for modulating inflammation and inducing apoptosis in fibroblast-like synoviocytes. Novel pharmacological agents—including salubrinal, STF-083010, and proteasome inhibitors—demonstrate disease-modifying potential in preclinical models. A detailed understanding of ERS signaling offers new perspectives for precision therapies in RA. Modulating the UPR may restore immune balance and reduce treatment resistance, highlighting ERS pathways as emerging therapeutic targets in autoimmune arthritis..

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1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory condition marked by repeated bouts of inflammation in the joints, typically affecting both sides of the body and commonly involving the hands, feet, and wrists. The active phase of RA involves a complex interplay between the body's innate and adaptive immune systems, leading to ongoing inflammation in the joint lining and sometimes affecting other organs, particularly in more severe cases [1]. The body's usual regulatory mechanisms often fail to control the production of self-reactive antibodies such as rheumatoid factor (RF) and anti-citrullinated protein/peptide antibodies (ACPA), also known as anti-cyclic citrullinated peptide antibodies (anti-CCP). This failure can activate B cells improperly and disrupt immune responses, potentially causing significant joint and bone damage, especially in the smaller joints of the hands and feet, along with systemic symptoms like fatigue, general discomfort, and musculoskeletal pain. The identification of these mechanisms offers hope for new treatments [2,3]. Yet, despite advancements in understanding and treating RA, some patients still do not respond well to current treatments. This review delves into the underlying causes of RA and examines the key signaling pathways involved, including those related to metabolic changes, to lay the groundwork for more targeted use of existing treatments and the development of new inhibitors targeting these pathways. A deeper understanding of RA's complex signaling pathways will enhance precision medicine approaches, particularly for those with hard-to-treat RA or multidrug-resistant forms of the disease [4,5].

2. THE ENDOPLASMIC RETICULUM AND ER STRESS

The Endoplasmic Reticulum (ER) plays a crucial role in synthesizing and folding about a third of all proteins in eukaryotic cells. Beyond these functions, it is also essential in various other processes including protein quality control, protein transport, lipid creation, storing intracellular calcium ions (Ca2+), and forming autophagic vacuoles. To ensure proteins fold correctly and avoid improper interactions or aggregation, the ER employs specialized molecular chaperones such as the 78-kDa glucose-regulated protein (GRP78) and the 94-kDa GRP (GRP94), lectin chaperones like calnexin and calreticulin, and folding enzymes including protein disulfide isomerases (PDIs) [6-8]. Despite these mechanisms, a significant portion of newly made proteins still misfold and are targeted for elimination through a process called ER-associated degradation (ERAD). This process involves the identification, targeting, ubiquitination, and retro-translocation of these misfolded proteins into the cytoplasm for destruction by proteasomes. Under conditions that increase protein production or introduce cellular stressors such as changes in redox status, depletion of ER calcium, lack of energy, insufficient autophagy, and heightened inflammation, the ER's capacity to degrade misfolded proteins can be overwhelmed. This leads to an accumulation of proteins within the ER lumen, a state referred to as ER stress. In response to ER stress, cells activate the Unfolded Protein Response (UPR) to manage the situation [9,10].

ER stress has been linked to the development of various disorders associated with human leukocyte antigen (HLA), such as RA and ankylosing spondylitis (AS). The HLA gene cluster, found on chromosome 6 p21.3, produces cell surface proteins crucial for presenting antigenic peptides. HLA alleles and haplotypes are key genetic contributors to numerous diseases, including RA, where the HLA-DRB1 gene locus plays a pivotal role in susceptibility [11,12]. It is well-documented that the majority of individuals with RA possess HLA-DRB1 alleles that encode a specific five-amino acid sequence known as the "shared epitope" (SE). Recent findings have shown that ER stress, induced by agents like lipopolysaccharide or dithiothreitol, causes the SE receptor calreticulin to move from the ER to the cell surface. This translocation leads to increased intracellular Ca2+ levels and activation of the peptidylarginine deiminase (PAD) enzyme, promoting protein citrullination — a key process in the onset of autoimmunity in RA. Additionally, experiments involving the injection of lipopolysaccharide into transgenic mice with a SE-coding DRB1 allele resulted in the production of ACPAs, elevated serum levels of tumor necrosis factor alpha (TNF-α), and bone damage [13-15].

Similarly, specific HLA-B27 alleles are significant genetic risk factors for AS. A proposed mechanism for HLA-B27's role in AS involves its propensity to misfold, leading to accumulation in the ER, ERAD, ER stress, and activation of the UPR. Studies in transgenic rats have demonstrated that HLA-B27 misfolding and subsequent UPR activation are associated with increased levels of the pro-inflammatory cytokine interleukin-23 (IL-23), suggesting a connection between HLA-B27 misfolding and immune system dysfunction [16,17].

3. RHEUMATOID ARTHRITIS AND ITS PATHOGENESIS

RA is a diverse condition characterized by the presence of ACPA/anti-CCP autoantibodies in about 70% of patients, according to most studies. These antibodies are highly specific to RA, with a specificity range of 87% to 98%, making them a reliable marker for diagnosing the disease. Additionally, the presence of shared epitope positive HLA-DR alleles is linked to both anti-citrullinated peptide antibodies and a genetic predisposition to RA, though the molecular reasons behind these links remain unclear [18,19].

Citrullination, the conversion of arginine into citrulline by PADs, plays a crucial role in RA's development. The regulation of this process is disrupted in RA, leading to increased activity. Normally, PAD enzymes are regulated by calcium levels and redox conditions to prevent overactivation. However, in RA, factors like perforins and bacterial toxins can cause a significant influx of calcium, triggering excessive PAD activity and citrullination within the joint [20-22]. Furthermore, the oxidative state of the synovial joint environment in RA tends to inactivate PADs, suggesting that ongoing citrullination requires the continual release of active enzymes from cells undergoing death, a process that may be exacerbated by the presence of PAD-activating autoantibodies [23].

PAD enzymes are deactivated outside of cells, and the presence of co-factors that activate PADs, alongside the constant release of active PAD enzymes from dying or activated cells, is essential for effective citrullination in RA. Thus, targeting the pathways that lead to excessive activation of PAD enzymes offers a promising strategy for preventing the expansion of the citrullinome in RA, potentially leading to clinical improvements for affected individuals [24,25].

Initial research indicated that a specific citrullinated peptide from vimentin, known as Vim R70Cit, might have a higher affinity for binding to HLA-DR molecules that possess the shared epitope compared to those that do not, potentially facilitating the presentation of citrullinated peptides to T cells and promoting the production of IgG ACPA. However, a comprehensive analysis examining the binding of 180 peptides, both citrullinated and non-citrullinated, spanning the entire alpha and beta chains of human fibrinogen, did not support the notion that citrullinated peptides have a superior binding affinity to HLA-DR molecules with the shared epitope over their non-citrullinated counterparts [26,27]. Additionally, it has been found that half of the patients with RA possess IgG autoantibodies against the peptidyl arginyl deiminase 4 (PAD4) enzyme, indicating the possible involvement of helper T cells that recognize PAD4 peptides. These T cells could

assist B cells targeting citrullinated epitopes on proteins modified by PAD4, following a hapten-carrier mechanism [28].

The precise causes of RA remain elusive, but it is clear that a combination of genetic and environmental factors plays a crucial role in triggering the disease. Genetic research in RA patients has identified critical factors, such as certain alleles at the HLA–DRB1 locus that feature a specific five amino acid sequence (QKRAA) at positions 70–74, known as the shared epitope [29,30]. Other genetic aspects include the selection of specific T-cell repertoires and the presentation of antigens; changes in peptide affinity may also contribute to the autoimmune reactions seen in RA. The outlook for RA patients who test positive for ACPA and/or RF is generally poorer compared to those without these antibodies. Additionally, neuro-immunological factors are implicated in the disease's progression [31,32].

Environmental risk factors identified in RA patients encompass smoking, silica exposure, periodontitis, and variations in gut microbiota. Gender is another significant risk factor, with the disease being three times more prevalent in women than in men [33,34].

Genetic, environmental, and epigenetic factors contribute to changes in the way genes are expressed and lead to modifications in the body's proteins, specifically in the process of citrullination. This results in the production of anti-citrullinated proteins such as α-enolase, keratin, fibrinogen, fibronectin, collagen, and vimentin, which are mistakenly identified as harmful by the immune system in individuals with RA [35,36]. Additionally, infectious agents and alterations in the gut microbiome are linked to the advancement of RA. An imbalance in the gut microbiota in those with RA can disrupt immune system responses, triggering the onset of the disease. The composition of the gut microbiota not only helps predict RA susceptibility but also presents potential targets for reducing RA incidence. The gut microbiota's enzymes and by-products can influence the effectiveness or toxicity of medications, either directly or indirectly. Conversely, certain drugs can alter the composition of the gut microbiota; for example, administering etanercept, which includes the TNF receptor, may help restore beneficial gut bacteria [37-39].

Changes in specific gut bacteria have been shown to correlate with both the progression of RA and how patients respond to treatment. Therefore, tailoring interventions to target the gut microbiota of each individual patient could reduce RA symptoms, enhance the effectiveness of treatments, and lead to better health outcomes. The distinct gut microbiota found in RA patients, as opposed to healthy individuals, underscores the significant role of gut dysbiosis in the development of RA. Diet, particularly its nutritional content, is one of the key environmental factors influencing the composition of the gut microbiota [40-42].

To mitigate and control inflammation levels in RA, adjusting the gut microbiota via dietary changes is advised. Specifically, adopting a Mediterranean diet can positively influence the gut microbiota, potentially leading to better RA management. The incorporation of probiotics containing Lactobacillus acidophilus and Lactobacillus casei has been found beneficial in decreasing RA disease activity, with an increase in bacillus spp. and other Lactobacillus species observed in the intestines of RA patients [43,44]. It appears that various Lactobacillus strains play distinct roles in the development and activity of RA. Additionally, transferring fecal microbiota from healthy individuals to RA patients may also diminish disease activity. The composition of gut microbiota might serve as markers for diagnosing RA, particularly in its early stages. In early RA, there's a notable reduction in advantageous gut bacteria like Bacteroidetes, with Prevotella copri becoming more prevalent and displacing other beneficial microbes. The oral microbiota also plays a crucial role in RA, where an imbalance can lead to periodontitis. The inflamed gums in such conditions contain proteins prone to citrullination and ACPA, with Porphyromonas gingivalis being a key player in protein citrullination and RA onset [45,46].

In a healthy state, the synovium comprises mesenchymal-derived fibroblast-like synovial cells (FLS) and macrophages. In RA, FLS exhibit unique behaviors such as increased proliferation, resistance to apoptosis, and the secretion of high levels of cytokines, chemokines, adhesion molecules, matrix metalloproteinases (MMPs), and their inhibitors, directly contributing to cartilage damage and persistent inflammation [47,48].

Studying the efficacy mechanisms of drugs used in RA treatment can provide deeper insights into the disease's pathogenesis. Methotrexate (MTX), a conventional synthetic disease-modifying antirheumatic drug (csDMARD), is commonly prescribed as an initial treatment for RA. MTX, which acts as a folic acid antagonist, inhibits DNA and RNA synthesis and reduces inflammation through various pathways in RA. Moreover, MTX enhances the effectiveness of anti-TNF therapies, beyond its role in lowering anti-drug antibody levels [49].

4. ERS IN RA

Cells exposed to internal and external damage triggers can activate endoplasmic reticulum stress (ERS) and trigger the UPR. The UPR is primarily controlled by three proteins: protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6). Under normal conditions, these proteins are bound to GRP78 in a non-covalent manner [50,51]. Upon the occurrence of ERS, GRP78 attaches to improperly folded proteins and detaches from PERK, IRE1, and ATF6. This detachment activates various signaling pathways that aim to halt DNA transcription and translation, stop the production of new proteins, and speed up the removal of faulty proteins, thereby helping the cell adjust to the internal environment. However, the UPR can also trigger pathways leading to cell death

through apoptosis, especially when damage is prolonged and severe, or when the interplay among pathways overwhelms the endoplasmic reticulum's capacity to manage misfolded proteins [52,53].

In studies related to RA, antibodies specific to GRP78 were detected in as many as 63% of RA patients, 7% of individuals with other rheumatic conditions, and only 1% of healthy individuals. Genes associated with ERS were found to be highly active in RA FLS and synovial macrophages. Laboratory studies showed that TNF and IL-1β elevated GRP78 levels in synovial cells. Suppressing GRP78 using siRNA halted the TNF- or TGF-β-driven growth of FLS and the increase of cell cycle protein D1, leading to cell death [54,55]. Conversely, high levels of GRP78 resulted in the proliferation of synovial tissue, which in turn stimulated more cytokine release, creating a harmful feedback loop. The same research indicated that GRP78 directly influences VEGF 165-driven angiogenesis. Recent findings also suggest that azithromycin can mitigate collagen-induced arthritis (CIA) in mice by inhibiting GRP78, highlighting its significant role in the persistence of chronic arthritis [56-58].

Upon separation from GRP78, PERK initiates its activation by dimerizing and autophosphorylating, which leads to the phosphorylation of the eukaryotic translation initiation factor 2α (eIF2α). This phosphorylation of eIF2α serves to halt mRNA translation, thereby reducing or pausing protein synthesis and easing the burden of protein folding in the ER. While eIF2α generally suppresses the translation of most proteins, it specifically facilitates the production of transcription factor 4 (ATF4) [59,60]. ATF4 then enhances the expression of the GRP78 gene, helping to restore balance within the endoplasmic reticulum and activating NF-κB, which plays a role in generating and releasing inflammatory molecules. In conditions of prolonged and intense ERS, ATF4's continuous overexpression triggers the activation of CHOP, a transcription factor pivotal for the transition from cell survival to apoptosis during ERS, by influencing Bcl-2/Bcl-Xl mediated apoptosis and encouraging cell death [61,62]. Notably, in RA synovial tissues, as opposed to those from healthy or osteoarthritis individuals, there is an upregulation of GRP78 and phosphorylated eIF2α. Salubrinal, which inhibits the dephosphorylation of eIF2α, has demonstrated efficacy in reducing pro-inflammatory cytokine release and Dusp2 gene expression in a mouse model of CIA, thereby mitigating arthritis. The ERS inducer thapsigargin (TG) has been shown to enhance osteoclastogenesis via NF-κB activation and reactive oxygen species (ROS) production triggered by RANKL, while IL-1β boosts osteoclast formation through RANKL by increasing GRP78, PERK, and IRE1 levels, a process that can be counteracted by 4-phenylbutyric acid (4-PBA). Furthermore, zinc ferrate nanoparticles and docosahexaenoic acid (DHA) have been identified as agents that induce apoptosis in RA FLS by targeting the PERK-ATF4-CHOP pathway [63].

ATF6, an ER type II transmembrane protein, dissociates from GRP78 under ERS conditions and relocates to the Golgi apparatus. Here, its N-terminal is cleaved, activating it before it moves to the nucleus to bind with the transcription factor XBP1 heterodimer, initiating the endoplasmic reticulum stress element (ERSE). This activation leads to the upregulation of genes like GRP94, GRP78, and ERP57, which accelerates the clearance of misfolded proteins within cells, reducing ERS. However, prolonged ERS causes ATF6 to stimulate the expression of apoptotic genes such as CHOP, leading to apoptosis [64,65]. Research into ATF6's role in RA is still emerging, but high ATF6 levels have been observed in RA synovium, and pro-inflammatory cytokines like IL-1β and TNF are known to induce ATF6 expression in RA-FLS. Tacrolimus, a crucial immunosuppressive drug for RA treatment, has been shown to decrease ATF6 expression, thereby lessening RA progression by inhibiting ERS-driven osteoclastogenesis and inflammation [66,67].

IRE1 is a type I membrane protein located in the ER that possesses endonuclease capabilities. It becomes activated, known as IRE1α, through a process of oligomerization and autophosphorylation after detaching from GRP78. This active form cleaves the mRNA of X-box binding protein 1 (XBP1), resulting in the generation of a spliced mRNA that is transported to the nucleus and translated into an active transcription factor, XBP1s [68,69]. Within the nucleus, XBP1s promotes the expression of the GRP78 gene, enhances the breakdown of misfolded proteins in the ER, reduces the synthesis of new proteins, and triggers the expression of the apoptosis-related gene CHOP. The IRE1α-XBP1s pathway also plays a role in splicing that leads to the secretion of cytokines dependent on toll-like receptors and sustains the activation cycle of FLS in an autocrine manner. Research on Litsea coreana flavonoids has shown their ability to block the IRE1/mTORC1/TNF-α-mediated inflammatory response in peritoneal macrophages of CIA mice, significantly reducing arthritis symptoms in a dose-responsive manner [70,71]. Studies on peripheral blood mononuclear cells (PBMCs) from patients with RA revealed elevated levels of GRP78, IRE1, and XBP1, indicating higher IRE1α activity in synovial macrophages compared to healthy individuals. Additionally, targeting IRE1 for knockdown was shown to halt the progression of inflammatory arthritis in mice. Investigations into the effects of zinc ferrate nanoparticles on RA-FLS highlighted the activation of the IRE1-XBP1 pathway as a mechanism to induce apoptosis, alongside the activation of the PERK-ATF4-CHOP pathway [72,73]. Furthermore, IRE1 is identified as a crucial element in B-cell differentiation, with the IRE1-XBP1 pathway regulating both B-lymphocyte maturation and the differentiation of antibody-producing plasma cells. These findings link the resistance to apoptosis in RA-FLS and the continuous presence of chronic inflammation to ERS, suggesting that overcoming this resistance may be crucial for unraveling the mechanisms underlying RA [74,75].

5. TARGETING ER STRESS-MODULATORY STRATEGIES IN RA

Potential targets that could be considered for the treatment of RA, focusing on both the inhibition and induction (up to a

death threshold) of the UPR as promising therapeutic approaches for various diseases [76,77].

6. GRP78/BIP

The targeting of GRP78/BiP for therapeutic purposes in RA is a debated topic due to its varied roles in specific autoimmune responses. Consequently, both suppressing and enhancing GRP78/BiP levels could potentially benefit RA treatment, depending on the particular clinical context. For patients with RA that is resistant to treatment, inhibiting GRP78/BiP might offer a viable strategy to mitigate the disease's harmful characteristics. Evidence from studies shows that mice with a deficiency in GRP78/BiP exhibit a reduction in CIA. Furthermore, reducing GRP78/BiP levels has been shown to significantly decrease VEGF-driven angiogenesis, curb the cytokine-induced proliferation of synoviocytes, and trigger apoptosis in FLS in RA mouse models [78,79]. The depletion of GRP78/BiP also notably impedes the migration and chemotaxis of endothelial cells, which are essential processes in angiogenesis. Thus, targeting both the extracellular and surface expressions of BiP could be an effective method for selectively addressing invasive RA-FLS. However, it's important to note the beneficial anti-inflammatory and resolution-promoting effects of GRP78/BiP, which can also be harnessed for RA treatment. In line with this, recombinant human GRP78/BiP is undergoing Phase I/II clinical trials for RA patients, showing encouraging results [80,81]. Additionally, among 42 examined 20-mer peptides for GRP78/BiP epitopes, the BiP456–475 peptide demonstrated notable immunoregulatory properties and therapeutic potential for RA. Oral administration of the BiP456–475 peptide exhibited minimal inhibitory effects on PBMCs from RA patients and promoted the expansion of regulatory T (Treg) cells through increased IL-10 production in CIA mice. [82,83]

7. IRE1A–XBP1

Treatment targeting the signaling pathway with specific inhibitors of IRE1a has shown to alleviate inflammation symptoms in RA. For instance, 4 m8C, which specifically inhibits the ribonuclease functions of IRE1a such as XBP1 splicing and RIDD, was demonstrated to reduce the production of proinflammatory cytokines triggered by TLR in RA mouse models. Another inhibitor, STF-083010, was effective in decreasing the survival of primary cultured human RA FLS and in diminishing synovial inflammation in the antigen-induced arthritis (AIA) mouse model. Furthermore, given that the activation of XBP1 serves as a critical junction for both hyper-ERAD and TLR-mediated inflammation – two pathways significantly involved in RA pathogenesis – targeting XBP1 could be a promising therapeutic strategy for RA [84,85].

8. PERK PATHWAY

Salubrinal acts as an indirect inhibitor of eIF2a dephosphorylation, aiding in cell protection against apoptosis caused by ER stress. This is achieved by increasing phosphorylated eIF2a levels, which further inhibits protein synthesis. Additionally, salubrinal's ability to alleviate rheumatoid arthritis (RA) symptoms is linked to its suppression of the dual-specificity phosphatase (Dusp 2), an enzyme responsible for dephosphorylating mitogen-activated protein kinases (MAPKs). When administered, salubrinal effectively hinders the production of inflammatory cytokines such as IL-2, IL-13, IL-1b, and TNF in immune cells and reduces inflammatory responses in mice with CIA [86].

9. ERAD AND AUTOPHAGY/PROTEASOME INHIBITORS

Synoviolin emerges as a strategic target for drug development within the ERAD pathway. Among synoviolin enzymatic inhibitors, LS-101 and LS-102, LS-102 demonstrates superior selectivity in targeting synoviolin and notably diminishes disease severity in in vivo RA models. Bortezomib, a selective inhibitor of the 26S ubiquitin-proteasome system, presents a viable treatment option for RA, especially for patients unresponsive to DMARDs [87-89]. This medication has been proven to inhibit TNF production and trigger apoptosis in activated T cells in RA patients. Furthermore, MG132, a novel proteasome inhibitor, has been observed to induce both ER stress and autophagy in RA-FLS when treated with thapsigargin, a potent ER stress inducer. The suppression of both autophagy (using chloroquine or 3-methyladenine) and proteasome (using epoxomicin and MG132) pathways significantly reduced the viability of RA-FLS, highlighting the therapeutic potential of targeting these pathways to overcome apoptosis resistance in RA-FLS [90,91].

10. OTHER POTENTIAL THERAPEUTIC OPTIONS

Certain ER chaperones, including calreticulin and glycoprotein 96, have the ability to move to the surface of the cell or even leave the cell during periods of cell stress. This movement can play various roles in the development of autoimmune diseases. For instance, the presence of GRP94 is elevated in the joints of individuals with RA and on the surface of macrophages [92,93]. Here, it can serve as a natural ligand for TLR2, aiding in the perpetuation of chronic inflammation. Moreover, when gp96 is found outside the cell, it can act as an autoantigen, triggering the production of autoantibodies and thus amplifying immune responses. As a result, targeting gp96 represents a promising new treatment strategy for RA patients. The Transient Receptor Potential Melastatin 7 (TRPM7) channel, part of the transient receptor potential channel family, possesses dual functions as both an ion channel and a protein kinase [94,95]. Its overexpression influences the survival of RA FLS under conditions of thapsigargin-induced ER stress. The suppression of TRPM7, either through

chemical inhibitors or specific siRNA, has been observed to increase the expression of CHOP and caspase-3, leading to apoptosis and a higher apoptosis rate in FLS. Therefore, a therapeutic approach that combines TRPM7 inhibitors with ER stress activators is being considered for RA treatment [96,97].

11. CONCLUSION

Rheumatoid arthritis is increasingly recognized as a disease in which endoplasmic reticulum stress (ERS) and the unfolded protein response (UPR) play central roles in sustaining inflammation, synovial hyperplasia, and autoimmunity. The persistent activation of ERS sensors—PERK, IRE1, and ATF6—promotes synovial fibroblast survival, cytokine release, and angiogenesis, while prolonged stress triggers apoptosis resistance that contributes to chronic disease progression. Dysregulation of GRP78/BiP and UPR components not only exacerbates inflammatory signaling but also links genetic susceptibility (notably HLA-DRB1 and HLA-B27 alleles) with immune tolerance breakdown and protein citrullination.

Targeting these maladaptive ER stress responses represents a promising therapeutic direction. Preclinical studies demonstrate that modulation of PERK-eIF2α-CHOP, inhibition of IRE1-XBP1 signaling, and pharmacological control of ERAD or autophagy can attenuate disease activity and promote apoptosis in rheumatoid fibroblast-like synoviocytes. Agents such as salubrinal, bortezomib, and small-molecule inhibitors of GRP78 or synoviolin illustrate the translational potential of this approach.

Future research should focus on defining the threshold between adaptive and pro-apoptotic ER stress responses in RA and developing targeted modulators that fine-tune UPR signaling without impairing essential cellular homeostasis. Integrating ER stress modulation with existing immunotherapies could improve disease outcomes and overcome multidrug resistance in difficult-to-treat RA.

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